REMARKS

Claim Amendments

Claims 114-151 have been canceled.

Claims 190, 199, 208, 217, 226, 229 and 232 have been amended to specify that the method, reaction mixture or kit are for amplification or reverse transcription of a target viral RNA and a reference RNA sequence. The claims have also been amended to delete the language "are of similar lengths and." In addition, the claims have been amended to change the language "by the same oligonucleotides or by different oligonucleotides" to read "by the same or different oligonucleotides."

Claims 190, 199, 208 and 217 have further been amended to delete the last step.

Claims 235-241 have been canceled.

New claims 249-255 have been added. These claims correspond to previous claims 190, 199, 208, 217, 226, 229 and 232 in which the language "are of similar lengths and" has been deleted and in which the language "by the same oligonucleotides or by different oligonucleotides" has been amended to read "by the same or different oligonucleotides." In addition, the term "relative" has been added in the last step of claims 249-252. Support for this language can be found at page 7, lines 6-8 of the present specification.

Applicants submit that these amendments do not constitute new matter and their entry is requested.

Summary of the Claims

Claims 190-234 and 242-248 are directed to processes for amplification of a target viral RNA sequence in a sample (claims 190-225, 241-245), an amplification reaction mixture (claims 226-228 and 246), a reverse transcription reaction mixture (claims 229-231 and 247) and a kit (claims 232-234 and 248). The process involve the simultaneous amplification of a target viral RNA sequence and a reference RNA sequence (claims 190-198, 208-216, 242 and 244) or involve first a simultaneous reverse transcription and then a simultaneous amplification of a target viral RNA sequence and reference RNA sequence (claims 199-207, 217-225, 243 and 245). The reference RNA sequence of claims 190-234 is a reference RNA sequence that

comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. The reference RNA sequence and the target RNA sequence can be amplified by the same or different oligonucleotides.

Claims 249-255 are directed to processes for quantitation of a target viral RNA sequence in a sample (claims 249-252), an amplification reaction mixture (claim 253), a reverse transcription reaction mixture (claim 254) and a kit (claim 255). The process involves the simultaneous amplification of a target viral RNA sequence and reference RNA sequence (claims 249 and 251) or involve first a simultaneous reverse transcription and then a simultaneous amplification of a target viral RNA sequence and reference RNA sequence (claims 250 and 252). The reference RNA sequence of claims 249-255 is a reference RNA sequence that comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. The reference RNA sequence and the target RNA sequence can be amplified by the same or different oligonucleotides.

Summary of the Invention

The present invention is directed to a method for the quantitation of target viral RNA in a sample by simultaneously amplifying a target viral RNA sequence and a known quantity of a reference RNA sequence as an internal standard. That is, the target viral RNA sequence, if present, and the reference sequence are simultaneously amplified in the same reaction mixture. The quantity of target viral RNA present in the sample is determined by comparing the amount of the amplified target viral RNA and the amount of the amplified reference RNA based on the known quantity of reference RNA added as an internal control. The reference RNA sequence may be (a) a reference RNA sequence that consists of the target viral RNA sequence with a multibase insert into a site within the target viral RNA sequence or (b) a reference RNA sequence that comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. In each instance, the reference RNA sequence and the target viral RNA sequence are of similar length and can be amplified by the same oligonucleotides or by different oligonucleotides.

Priority

The Examiner has concluded that the priority applications have support for amplifying reference and target RNA sequences using different oligonucleotide primers either simultaneously or in separate amplification reaction. However, the Examiner contends that the limitation "amplified by the same oligonucleotides" does not have support in the prior application. Thus, the Examiner contends that the instant application does not get the claimed priority to any of the prior applications. Applicants submit that the Examiner is in error.

Applicants submit that Serial No. 07/148,959, filed 27 January 1988 provides clear support for the amplification of reference and target RNA sequences using the same oligonucleotides. Specifically, page 3, lines 23-26 of the '959 application states:

> A fourth primer to provide an additional aid to quantitation of virus levels is provided by a reference RNA which **can be amplified** and detected **by the same oligonucleotides** used for authentic virus RNA samples. (emphasis added).

The '959 application then describes a maxigene reference RNA and describes its use as an internal control and an additional aid to quantitation. See, page 3, line 26 – page 4, line 14 and page 5, lines 1-8 of the '959 application. In addition, Example III of the '959 application discloses that this reference RNA is included in the target samples.

Thus, Applicants submit that the clear language of the '959 application provides support for amplifying reference and target RNA sequences using the same oligonucleotides. Accordingly, Applicants are entitled to the priority of Serial No. 07/148,959, filed 27 January 1988.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 114-248 under 35 U.S.C. § 112, second paragraph for being indefinite. The Examiner states that the independent claims 114, 130, 138, 146, 150, 190, 199, 208, 217, 226, 229 and 232 recite reference sequence with a multibase insert. The Examiner contends that the claims are unclear and indefinite because it is not clear how the reference sequence and the target viral RNA sequence are of similar lengths when the language of the claim states that the reference sequence contains a multibase insert which indicates that the

reference RNA sequence is longer. Applicants traverse this rejection as it may apply to any of the currently pending claims.

First, Applicants note that only independent claims 114, 122, 130, 138, 146, 148 and 150 include the language "multibase insert" and that this language is not present in the remaining independent claims noted in this rejection. Since the language recited by the Examiner is not present in these latter independent claims, Applicants submit that the Examiner's reasons for the rejection of these claims is not appropriate.

Second, Applicants submit that the fact that the reference RNA sequence in independent claims 114, 122, 130, 138, 146, 148 and 150 contains a multibase insert and is of similar length to the target RNA sequence does not render claims 114-151 and 235-241 indefinite. As the Examiner is well aware, definiteness is determined with reference to a person of ordinary skill in the art. *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875, 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994) ("The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification."); *In re Warmerdam*, 33 F.3d 1354, 1361, 31 U.S.P.Q.2d 1754, 1759 (Fed. Cir. 1994) ("The legal standard for definiteness is whether a claim reasonably apprises those of skill in the art of its scope."). Applicants submit that the claimed subject matter is definite to the skilled artisan, particularly when read in light of the specification.

Specifically, the instant specification (as well as Serial No. 07/148,959, filed 27 January 1988) describes a maxigene as the selected target sequence with a multibase pair insert into a unique site. The specification provides an example of a maxigene in which a 21 base pair insert is made in the HIV-1 3' ORF (nef) region which creates a reference sequence that is 21 bases longer than the target sequence. In addition, the specification discloses that a reference sequence is made for HCMV by making a small insertion into the target RNA sequence. As is evident in the word itself, "multibase" means anything more than one, and thus could be as few as two nucleotides. The only example in the specification is a maxigene with a multibase insert of 21 nucleotides. Applicants submit that a small insertion would be considered by the skilled artisan to be less than a 21 nucleotide insertion, and in any event probably not much more than 21 nucleotides. Applicants submit that these examples provide sufficient guidance to the skilled

artisan as to the meaning of the term "of similar length" in the context of a reference RNA sequence that contains a multibase insert.

Although Applicants submit that claims 114-151 and 235-241 as previously presented are definite, they have nevertheless canceled them in this amendment in order to expedite the prosecution of this application.

Although Applicants submit that claims 190-234 and 242-248 as previously presented are not subject to the reasons for this rejection as set forth by the Examiner in the Office Action of 17 March 2008 because they do not contain the language "multibase insert," they have nevertheless amended these claims to delete the language "of similar length" in order o expedite the prosecution of the application.

Rejection Over Wang et al.

In the Office Action dated 17 March 2008, the Examiner rejected claims 114, 115, 117, 118, 120, 122, 123, 125, 126, 128, 130, 131, 133, 134, 136, 138, 141, 142, 144, 146-151, 190-192, 194, 195, 197, 199-201, 203, 204, 206, 208-210, 212, 213, 215, 217-219, 221, 222, 224 and 226-248 under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727). Applicants do not generally disagree with the Examiner's analysis of Wang et al. However, Applicants submit that the claimed subject matter **does not require** the use of a shared primer pair, as was held by the BPAI in Interference No. 105,055. Since the claimed subject matter **does not require** the use of a shared primer pair, Wang et al. is not prior art under 35 U.S.C. § 135(b).

Applicants have canceled claims 114, 115, 117, 118, 120, 122, 123, 125, 126, 128, 130, 131, 133, 134, 136, 138, 141, 142, 144, 146-151 and 235-241 which obviates this portion of the rejection.

Applicants have amended independent claims 190, 199, 208, 217, 226, 229 and 232 (and hence the depended claims 191, 192, 194, 195, 197, 200, 201, 203, 204, 206, 209, 210, 212, 213, 215, 218, 219, 221, 222, 224, 227, 228, 230, 231, 233, 234 and 242-245) such that they are not directed to quantification of a target RNA, but are directed to an amplification of both a target RNA and a reference RNA. In view of these amendments, Applicants submit that these claims

are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727). Withdrawal of this rejection with respect to these claims is requested.

With respect to new claims 249-255, Applicants submit that these claims are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727) in view of the Board's decisions Interference No. 105,055. First, Applicants submit that the Board's decision on Wang preliminary motion 1 (Paper 36 dated 5 November 2003 and titled Memorandum Opinion and Order) held that that Applicants are not claiming the same subject matter as claimed in the Wang et al. '727 patent. Applicants' basis for this contention is fully set forth in the Amendment filed 6 December 2007. As discussed in that Amendment the Board stated, "the dispositive question is whether 'a reference RNA which **can be amplified and detected by the same oligonucleotides** as used for authentic virus RNA samples' necessarily **requires** or results in the use of a shared primer pair." (Memorandum Opinion and Order, p. 20; emphasis added) The Board concluded that there was no disclosure in the specification that the preselected site should be chosen to avoid disrupting primer binding sites. (Memorandum Opinion and Order, pp. 21-22.) Thus, the Board concluded that although the Murakawa et al. earlier claims "encompass use of a shared primer pair, they **do not require** or necessarily result in use of a shared primer pair." (Memorandum Opinion and Order, p. 22; emphasis added.) In this regard, the Board stated "[I]t is possible to have a maxigene control sequence which can be amplified by different primers and detected by the same oligonucleotides used for the target sequence." (Memorandum Opinion and Order, p. 22.) The Board concluded that "binding to a shared primer pair is **neither excluded, required nor a necessary result**" in any of the Murakawa et al. earlier claims. (Memorandum Opinion and Order, p. 22; emphasis added.) Thus, the BPAI concluded that none of the earlier Murakawa claims are directed to the same or substantially the same invention as claimed in Wang et al. (Memorandum Opinion and Order, pp. 22-23.) These earlier claims included claims that, when read in light of the specification, include a reference RNA that can be amplified and detected by the same oligonucleotides as the target RNA.

Thus, the Board specifically held that the language relied upon by the Examiner in making the rejections in the present Office Action, i.e., "can be amplified and detected by the same oligonucleotides," **did not require** or necessarily result in the use of a shared primer pair.

Thus, Applicants submit that the Board has held that this language **does not require** the use of a shared primer pair in direct contrast to the Examiner's contention. Because the claims do not require the same primer pair, they are not barred by 35 U.S.C. § 135(b).

Furthermore, Applicants note that the final step in claims 249-252 recite determining the relative amount of the target viral RNA sequence present in the sample before amplification. This step was one of the steps that the Board noted was different than the corresponding step in the Wang et al. '727 patent in concluding that Wang et al. '727 claim 1 was not obvious over Murakawa's proposed claim 50 in combination with the prior art. *See*, page 25 of Paper 47 dated 5 April 2004 and titled Decision on Preliminary Motion. For the above reasons, Applicants submit that claims 249-255 are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727).

Rejection Over Wang et al. in view of Mullis et al.

In the Office Action dated 17 March 2008, the Examiner rejected claims 116, 119, 121, 124, 127, 129, 132, 135, 137, 139, 140, 143, 145, 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 under 35 U.S.C. § 135(b) over Wang et al. in view of Mullis et al. (US 4,683,195).

Applicants have canceled claims 116, 119, 121, 124, 127, 129, 132, 135, 137, 139, 140, 143, 145 which obviates this portion of the rejection.

Applicants have amended the independent claims from which claims 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 depend such that they are not directed to quantification of a target RNA, but are directed to an amplification of both a target RNA and a reference RNA. In view of these amendments, Applicants submit that these claims are patentable under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727) in view of Mullis et al. Withdrawal of this rejection with respect to these claims is requested.

Concluding Comments

In view of the above amendments and remarks, it is submitted that the claims are fully supported by the instant application, entitled to a priority date of at least 27 January 1988 and are patentable over the prior art of record. Reconsideration of this application and early notice of

allowance is requested. The Examiner is invited to telephone the undersigned if it will assist in expediting the prosecution and allowance of the instant application.

Respectfully submitted,

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